Introduction and Regulatory Reference Sheet
Circulatory System Devices Panel
May 7, 2014

On May 7, 2014, the Circulatory System Devices Panel (the panel) will discuss and make recommendations regarding the classification of membrane lung for long-term pulmonary support [extracorporeal membrane oxygenator – ECMO] specifically for the adult pulmonary and cardiopulmonary indications.

This device type is a preamendment Class III device, meaning that this device type was marketed prior to the Medical Device Amendments of 1976 and was classified by the original classification panels as Class III. To date, the FDA has not established an effective date for the requirement for premarket approval (PMA) so these devices may proceed to market via the premarket notification [510(k)] process until such time as the classification steps are completed.

On April 9, 2009, the FDA issued an order under section 515(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requiring safety and effectiveness information on ECMO devices (74 FR 16214, April 9, 2009). This information will be used to determine whether the classification should be revised to require a PMA application (Class III) or whether the device should be down-classified into Class I (General Controls) or Class II (General and Special Controls). In response to that order, FDA received information in support of reclassification from one device manufacturer who recommended ECMO devices be reclassified to Class II. The manufacturer stated that safety and effectiveness of these devices may be assured by special controls.

On January 8, 2013, FDA issued a proposed order (78 FR 1158) recommending that the current regulation for membrane lung devices for long-term pulmonary support be redefined to include all components of an extracorporeal circuit for long-term use (ECMO). Furthermore, FDA proposed that these devices be reclassified from Class III (PMA) to Class II (Special Controls) for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery.

The proposed order provided for a comment period that was open until April 8, 2013. FDA received three public comments concerning the proposed reclassification.

On September 12, 2013, FDA and the Circulatory System Devices Advisory Committee convened to discuss the classification of the membrane lung for long-term pulmonary support (21 CFR 868.5610) in the pediatric cardiopulmonary and failure-to-wean patient populations. The Panel agreed with the reclassification proposal to Class II for the pediatric population as identified above, but recommended that FDA convene another Panel to discuss the clinical uses of ECMO for adult pulmonary and cardiopulmonary indications. The Panel requested that FDA review the available literature in the adult population, and include this information when considering the overall classification proposal for the membrane lung for long-term pulmonary support (21 CFR 868.5610).

At this meeting, the panel will be asked to discuss the classification of ECMO devices for adult pulmonary and cardiopulmonary indications. The panel will discuss the different intended uses for ECMO in the adult population, the risks to health, the available safety and effectiveness information, and possible special controls. After this advisory panel meeting, the FDA will consider all available scientific evidence and the input from panel members in determining whether to finalize the proposed reclassification or take some other action.

What data should be considered when making a classification recommendation?

Initial classification and reclassification recommendations are based on existing information for legally marketed devices and their predicates. Although information on future technology or new indications applicable for these devices may be available, this information is not relevant to the deliberations of the panel.

What are the definitions of Class I, Class II and Class III?

Federal law (Federal Food, Drug, and Cosmetic Act, section 513), established the risk-based device classification system for medical devices. Each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness.

As device class increases from Class I, to Class II to Class III, the regulatory controls also increase, with Class I devices subject to the least regulatory control, and Class III devices subject to the most stringent regulatory control.

The regulatory controls for each device class include:

- Class I (low to moderate risk): General Controls
- Class II (moderate to high risk): General Controls and Special Controls
- Class III (high risk): General Controls and Premarket Approval (PMA)

Class I, General Controls

A device is Class I if general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device. Examples of general controls are: registration and listing, medical device reporting, labeling and good manufacturing practices (GMPs). Devices may also be considered Class I if the device "is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and does not present a potential unreasonable risk of illness or injury."[1] Most Class I devices are exempt from submitting a 510(k). Examples of Class I cardiovascular devices include stethoscopes and cardiovascular surgical instruments.

[1] See Section 513(a)(1)(A) of the FD&C Act.

Class II, General and Special Controls

A Class II device is "a device which cannot be classified as a Class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance."[2] Examples of special controls are: performance standards, postmarket surveillance, patient registries, special labeling requirements, and development and dissemination of guidelines. Special controls may also include specific types of performance testing (e.g., biocompatibility, sterility, electromagnetic compatibility, pre-clinical testing) or labeling, which FDA may outline in the regulation or a special controls guideline. Most Class II devices require clearance of a 510(k) prior to marketing. Manufacturers are required to submit valid scientific evidence in their 510(k) demonstrating that the device is as safe and effective as a predicate device. Companies submitting a 510(k) for a device must demonstrate how any specified special controls have been met in order to receive marketing clearance. Examples of Class II cardiovascular devices include blood pressure cuffs and alarms, percutaneous catheters, catheter introducers and guidewires, and electronic stethoscopes.

Class III, General Controls and Premarket Approval

A Class III device is a device which:

1. "cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device," **and**
2. "cannot be classified as a class II device because insufficient information exists to determine that the special controls…would provide reasonable assurance of its safety and effectiveness," **and**
3. "is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health," **or**
4. "presents a potential unreasonable risk of illness or injury."[3]

Class III devices require premarket approval prior to marketing the device and must provide valid scientific evidence to demonstrate that the device has demonstrated a reasonable assurance of safety and effectiveness through the submission of a PMA application. Examples of Class III cardiovascular devices include cardiac stents, prosthetic heart valves, and VADs.

What will the Panel be asked to consider in determining which device class to recommend?

Risks to Health

The FDA will present the risks to health that they have identified to be associated with use of the device type. Some of these risks to health may have been identified by previous classification panels and some may have been identified by FDA and/or the manufacturers in response to the 515 Orders. The panel will be asked to comment on whether they disagree with inclusion of any

[2] See Section 513(a)(1)(B) of the FD&C Act.
[3] See Section 513(a)(1)(C) of the FD&C Act.

of the identified risks or whether they believe any other risks should be considered for each device type.

Safety and Effectiveness

The FDA will present available information regarding the safety and effectiveness of each device type. The panel will be asked to comment on the adequacy of the available scientific evidence with respect to safety and effectiveness for each device type and to determine whether the probable benefits to health from use of the devices for specific indications outweigh the probable risks. If safety and/or effectiveness are not established for each device type, or specific indications or technology of the device type, PMAs should be required to establish safety and effectiveness.

Special Controls

The FDA will present proposed special controls for those indications or technologies that they believe have established safety and effectiveness. The panel will be asked to comment on the adequacy of these proposed special controls in providing a reasonable assurance of safety and effectiveness in light of the available scientific evidence. The panel will also comment on whether any additional special controls should be proposed. If special controls can mitigate the identified risks to health, and safety and effectiveness have been established, it would be appropriate to recommend down-classification of the device types to Class II(special controls) in conjunction with general controls.

What is a "reasonable assurance of safety"?

As defined in 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury

What is a "reasonable assurance of effectiveness"?

As defined in 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when

accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

What are the practical implications of maintaining this device type in Class III?

If FDA issues a final order calling for PMAs for ECMO devices, manufacturers wishing to continue to market existing devices of this type must file a premarket approval (PMA) application within the specified timeframe that is designated in the final classification order. To support approval, the information in the PMA would have to demonstrate a reasonable assurance of safety and effectiveness. New devices or changes to existing devices would require approval of a PMA or PMA supplement. If a company does not file a PMA within the specified timeframe or otherwise does not receive an approval order for their product, the products are considered to be misbranded and should be removed from the market.

What happens if FDA decides to down-classify this device type into Class II?

If ECMO devices are down-classified, these devices would continue to be subject to the premarket notification [510(k)] requirements and any special controls specified in the final classification order. Companies with existing legally marketed devices would be subject to the newly defined special controls, and must ensure that their existing products meet all specified requirements. New devices and changes to existing devices that require a new submission to FDA would require a 510(k), demonstration that the special controls have been met, and a substantial equivalence (SE) determination.

What happens if FDA decides to split the classification for this device type?

In some situations, FDA may find it appropriate to split the classification of a device type by indications for use and/or device technologies. For example, FDA may determine that some technologies currently included within the classification regulation are not supported by available safety and effectiveness information or special controls cannot be established to mitigate the risks to health from use of the device type. As a result, FDA may choose to split a classification regulation and maintain the Class III classification (call for PMAs) for certain indications and/or device technologies and down-classify to Class II (special controls) other technologies currently within the same classification regulation.

What are the practical differences between PMA (Class III) and 510(k) (Class II) requirements?

A PMA application must provide all evidence to independently demonstrate a reasonable assurance of safety and effectiveness of the device. PMAs typically involve data from clinical

trials of the specific device that support both safety and effectiveness, as well as detailed manufacturing information for the device. Conversely, a 510(k) submission can leverage existing information on predicate devices, including applicable clinical data, to support marketing clearance. For devices subject to 510(k), the premarket submission need only provide evidence that the device has indications and technological characteristics consistent with existing legally marketed predicate devices and meets any required special controls.

Once a PMA is approved, the PMA holder must report all design, manufacturing, and labeling changes made to the approved device to FDA via PMA supplements[4] and PMA annual reports[5]. PMA holders are also typically subject to ongoing postmarket requirements. 510(k) holders are not subject to as stringent postmarket oversight. For example, for 510(k) devices, companies do not need to submit many types of minor changes to a device or its labeling to FDA for review nor do they need to submit manufacturing changes or annual reports.

Regardless of the classification of these device types, FDA does not regulate the practice of medicine, specifically, which devices clinicians can use and how they use them.

Why is this device type in the most stringently regulated Class III classification, but currently reviewed by FDA via the premarket clearance (510(k)) process?

When FDA's medical device regulation program began in the late 1970s, FDA regulated over 170 Class III device types through the 510(k) program. The intent was that FDA's regulation would be temporary and that, over time, FDA would decide to reclassify those device types (or regulations) into Class I or II, or to sustain the classification in Class III and call for PMA applications. Over the years, FDA has made significant progress in this original list; however, as of 2009, 26 medical device classification regulations, including the classification regulation for ECMO devices, remained in this transitional state awaiting final classification. This panel meeting is the result of FDA's ongoing 515 Program Initiative to facilitate the final adjudication of these remaining Class III device types. Based on recent legislative changes made to the Federal Food, Drug and Cosmetic Act through the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, FDA is now required to hold a meeting of a device classification panel prior to finalizing the reclassification of a device type. FDA is seeking panel input on ECMO devices to inform FDA's recommendation regarding the appropriate regulatory classification for this device type.

[4] Refer to FDA's Guidance for Industry and FDA Staff: 30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080192.htm).

[5] Refer to FDA's Draft Guidance for Annual Reports for Approved Premarket Approval Applications (PMA) http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089381.htm .

May I recommend a final classification of Class I or Class II, even if the device is eligible for Class III?

Although a device may be eligible for classification as a Class III device, you may still find that there is sufficient information (valid scientific evidence) to determine that general controls alone (Class I), or general controls and the application of special controls (Class II), can provide reasonable assurance of safety and effectiveness of the device. If this is the case, then you may recommend that the device be classified into a class other than Class III. In this scenario, then you should provide a rationale that summarizes the valid scientific evidence supporting your recommendation, and identifies the controls you believe are sufficient to provide reasonable assurance of safety and effectiveness.